



Regional Drug and
Therapeutics Centre

DRUG THERAPY FOR COPD

BNF Category: 3.1 & 3.2

NICE: CG101

PBR Status: In tariff

Tiotropium inhalation solution (marketed in 2007) and, more recently, inhaled indacaterol and oral roflumilast have been licensed for use in chronic obstructive pulmonary disease (COPD). Data on their use and long term safety are limited. Until further safety data are available, tiotropium inhalation solution should be prescribed with caution in people with cardiac rhythm disorders. Its use should only be considered for those with difficulties using the dry powder device. Roflumilast should not be routinely prescribed as its effectiveness when added to optimized NICE-recommended therapy in severe COPD has not been established. Once-daily indacaterol provides an additional option in mild COPD. It is not available as a combined ICS/LABA inhaler as recommended by NICE for use in moderate to severe COPD or when stepping up therapy in mild disease.

Background

COPD is characterised by airflow obstruction that is not fully reversible and is usually progressive in the long term.¹ It can result in significant disability and impaired quality of life. Smoking is the main cause of COPD.¹ Around three million people are estimated to be affected by COPD in the UK with most diagnosed in their fifties¹. It is the fifth leading cause of death (around 30,000 deaths annually) and the second largest cause of emergency hospital admissions.¹

What drug therapy is recommended by NICE?

NICE recommends the following stepwise strategy:¹

- For breathlessness or exercise limitation, a short-acting beta-agonist or muscarinic antagonist is indicated.
- For exacerbations or persistent breathlessness in people with a FEV₁ ≥ 50%, a long-acting muscarinic antagonist (LAMA) or a long acting beta-agonist (LABA) should be used. If the FEV₁ is < 50%, a LAMA or a combined inhaled corticosteroid (ICS)/LABA inhaler is recommended.
- For persistent exacerbations or breathlessness, a combined ICS/LABA inhaler should be used alone or with a LAMA ('triple therapy'). Combining a LABA and a LAMA ('dual therapy') should only be considered if an ICS is unsuitable.
- Oral theophylline should only be used after a trial of short-acting and long-acting bronchodilators or in people who are unable to use inhaled therapy.

What products have been introduced recently?

A new formulation of tiotropium (a LAMA) as an inhalation solution (Spiriva Respimat[®]) has been available since October 2007,² in addition to the previously available single-dose dry powder inhaler (Handihaler[®]). The drug is delivered as a fine mist via a multi-dose device. It is licensed as maintenance therapy to relieve COPD symptoms.²

Indacaterol (Onbrez Breezhaler[®]) is a once-daily LABA indicated for maintenance bronchodilator treatment of airflow obstruction in adults with COPD.³ It is formulated as dry powder capsules for use in an inhaler.

Roflumilast (Daxas[®]) is an oral selective phosphodiesterase-4 [PDE-4] inhibitor licensed as add on to bronchodilator therapy for the maintenance treatment of severe COPD (FEV₁ post-bronchodilator < 50% predicted) associated with chronic bronchitis in adults with a history of frequent exacerbations.⁴

What is the evidence for their use in COPD?

Tiotropium Inhalation solution

Compared to placebo and ipratropium, a meta-analysis (9 randomized controlled trials [RCTs] lasting six to 48 months, n = 13103) reported that tiotropium dry powder inhaler produced statistically significant but clinically small reductions in exacerbation and hospitalisation rates.⁵ The evidence for tiotropium inhalation solution is more limited. In people with stable moderate to severe COPD, three double-blind RCTs found tiotropium inhalation solution (5 micrograms daily for 48 weeks) to be more effective than placebo in improving the mean trough FEV₁ response and exacerbation rate.^{6,7} However, one study (n = 1990) was not powered for exacerbation outcomes,⁶ while the other study (n = 3991) only reported a small difference in the mean rates of any exacerbations.⁷

Four small, short-term, double-blind studies reported the inhalation solution to be non-inferior to the dry powder formulation in terms of lung function outcomes.⁸⁻¹⁰ Results for pharmacokinetic and adverse effects outcomes were comparable for both formulations.⁸⁻¹⁰

Indacaterol

Indacaterol was compared with placebo, tiotropium or twice-daily LABAs (fometerol or salmeterol) in three double-blind RCTs lasting 26 weeks or one year.¹¹⁻¹³ It was more effective than placebo in producing clinically relevant improvement in lung function outcomes. Compared to twice-daily LABAs and tiotropium, smaller absolute differences in lung function improvement outcomes were reported in favour of Indacaterol but the differences were of uncertain clinical significance. Reliable conclusions regarding relative effects on exacerbation frequency cannot be drawn from these studies.

Roflumilast

Compared to placebo, a recent Cochrane systematic review found that the oral PDE-4 inhibitors, roflumilast (nine RCTs, n = 9211) and cilomilast (14 RCTs, n = 6457), produced modest improvements in lung function which are below the level generally considered clinically relevant.¹⁴ Overall, patients randomised to PDE-4 treatment were less likely to have an exacerbation. Two 24-week RCTs, which allowed concomitant salmeterol or tiotropium use, were too short in duration to detect an effect on exacerbation outcomes.^{14,15}

In the Cochrane review, only one RCT (lasting one year) allowed concomitant inhaled corticosteroid use and it found no difference

in exacerbation outcomes between roflumilast and placebo.^{14,16} Although a statistical difference was reported in a post-hoc analysis (which pooled data from this and an unpublished trial), exacerbation rates were low (0.7 to 0.9 exacerbations per patient/year) and an absolute difference of 0.17 exacerbations per patient/year is of doubtful clinical significance.¹⁷

No trials of roflumilast as an add-on to triple or dual therapy (reflecting NICE recommendations) or comparing it with theophylline (a non-selective PDE-4 inhibitor) were identified.

How safe are they?

Long-term safety data for these products are lacking. Both the MHRA and a recent meta-analysis have highlighted a significant excess in mortality (particularly in people with cardiac rhythm disorders) with tiotropium inhalation solution, when compared with placebo.^{18,19} In contrast, tiotropium dry powder inhaler is associated with a decrease in all-cause mortality.^{18,20} A study comparing these two tiotropium formulations to assess the safety of the Respimat[®] formulation is ongoing.²¹

Indacaterol has a similar adverse effect profile to the twice-daily LABAs, salmeterol and formoterol.^{12,13} Naso-pharyngitis, cough, headache and upper respiratory tract infections were reported more frequently with indacaterol than placebo.^{3,11-13}

Gastrointestinal adverse effects (e.g. abdominal pain and diarrhoea) and headaches are common with roflumilast.^{4,14} Weight loss associated with treatment is of concern.¹⁴ Low body

mass index is a marker for poor prognosis in COPD.[1] Regular weight monitoring for under-weight patients is recommended.⁴

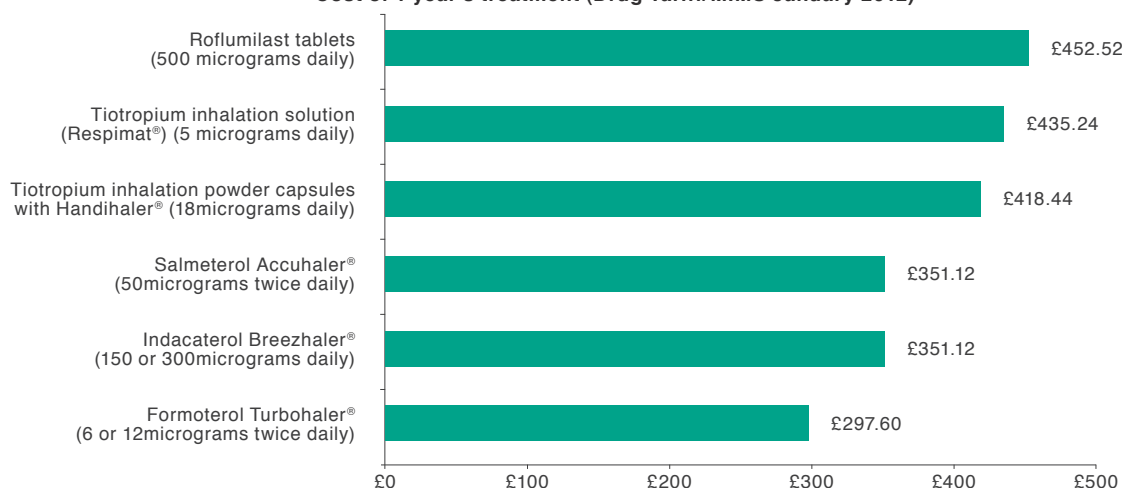
When should they be used?

As there is no evidence that tiotropium inhalation solution offers significant clinical advantages over the dry powder device, it should only be considered for people who have difficulties using the dry powder device. It should be prescribed with caution in people with cardiac rhythm disorders.¹⁸

Indacaterol provides an additional therapeutic option in mild COPD (FEV₁ ≥ 50%) if a LABA is indicated. It may be considered if compliance with a twice-daily LABA inhaler is poor. A combined ICS/LABA inhaler is recommended by NICE for use in moderate to severe COPD or when stepping up therapy in mild disease, but such a product is not currently available for indacaterol. Separate indacaterol and ICS-only inhalers (unlicensed for COPD) will be less convenient and more expensive than combined alternatives.

The place for roflumilast in current practice is uncertain and therefore it should not be prescribed routinely. Its effectiveness in severe COPD has not been established when added to optimised NICE recommended therapy. Roflumilast is considerably more expensive than inhaled therapy. A NICE Technology Appraisal recommends use only in the context of a clinical trial.²² People currently receiving roflumilast should have the option to continue treatment until they and their clinicians consider it appropriate to stop.²²

Cost of 1 year's treatment (Drug Tariff/MIMS January 2012)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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